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Continuati n of U.S. 08/901,225 IMMEDIATELY

96-368-4 IRVN001DIV2 GET-4

Cancer Immunotherapy using Autologous Tumor Cells Combined with Allogeneic Cytokine-Secreting Cells

J.C. Hiserodt et al., University of California

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Proposed Claims:

31. A method of stimulating an anti-tumor immune response or treating a neoplastic disease, comprising administering to a subject a composition comprising either a an allogeneic cell genetically altered to produce a cytokine at an elevated level, or the progeny of such a cell, wherein the cytokine is stably associated in the cell outer membrane.

32. The method of claim 31, wherein the cytokine is selected from the group consisting of IL-4, GM-CSF, IL-2, TNF-α, and M-CSF.

33. The method of claim 31, wherein the cell is a cancer cell.

34. The method of claim 31, wherein the cell is from a cancer of the same tissue type as a tumor in the subject.

35. The method of claim 3, wherein the cancer is an ovarian cancer or a brain cancer.

36. The method of claim 31, wherein the cell is allogeneic to the subject.

37. The method of claim 31, wherein the cell is histocompatibly identical to the subject.

38. The method of claim 31, wherein the composition further comprises a tumor-associated antigen, and wherein the combination of the cytokine and the tumor-associated antigen in the composition is effective in treating a neoplastic disease or eliciting an anti-tumor immunological response in the subject.

~~39. The method of claim 38, wherein the tumor-associated antigen is obtained from a cell autologous to the subject.~~

40. The method of claim 38, wherein the tumor-associated antigen is expressed by the same cells expressing the membrane-associated cytokine.

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41. The method of claim 38, wherein the composition comprises a combination of:
a) the cell expressing the membrane-associated cytokine; and
b) a tumor cell autologous to the subject;
wherein the combination is effective in treating a neoplastic disease or eliciting an anti-tumor immunological response in the subject.

42. The method of claim 41, wherein the tumor cell is a primary tumor cell dispersed from a solid tumor obtained from the subject.

43. The method of claim 41, wherein the tumor cell is a glioma, a glioblastoma, a gliosarcoma, an astrocytoma, or an ovarian cancer cell.

44. The method of claim 41, wherein the tumor cell is inactivated.

45. The method of claim 31, wherein the cell expressing the membrane-associated cytokine is inactivated.

46. The method of claim 31, wherein the cell produces a secreted cytokine in addition to the cytokine stably associated in the outer membrane.

47. The method of claim 31, wherein a majority of the cytokine produced by the cell is present on the outer membrane of the cell.

48. The method of claim 38, wherein the cytokine is selected from the group consisting of IL-4, GM-CSF, IL-2, TNF-α, and M-CSF.

49. The method of claim 31, wherein the composition comprises at least two cells, each of which has been genetically altered to produce a different cytokine at an elevated level, or is the progeny of such a cell, and wherein each cytokine is stably associated in the outer membrane of the cell.

50. A method of stimulating an anti-tumor immune response or treating a neoplastic disease, comprising administering to a subject a composition comprising a tumor associated antigen and a population of cells expressing a transmembrane cytokine at a level sufficient to stimulate an immune response to the tumor associated antigen in the subject.

51. The method of claim 31, wherein the cell is a human cell.

52. The method of claim 31, wherein the cytokine naturally occurs as a membrane cytokine.

53. The method of claim 31, wherein the cytokine is a fusion protein comprising a heterologous transmembrane region.

54. The method of claim 31, wherein the cell has been transduced with a retroviral expression vector, or is the progeny of such a cell.

55. The method of claim 31, which is a method for stimulating a primary immune response.

56. The method of claim 31, which is a method for stimulating a secondary immune response.

57. The method of claim 31, which is a method for treating a neoplastic disease.

58. The method of claim 31, further comprising providing the cytokine expressing cell that is present in the composition.

59. The method of claim 38, further comprising providing the tumor associated antigen that is present in the composition.

60. The method of claim 31, further comprising transducing a cancer cell with an expression vector encoding the membrane-associated cytokine.

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Continuation of U.S. 08/901,225

96-368-3 IRVN001DIV1 GET-3 1349

Cancer Immunotherapy using Autologous Tumor Cells Combined with Allogeneic Cytokine-Secreting Cells

J.C. Hiserodt et al., University of California

Claims:

31. A pharmaceutical composition comprising a human cell genetically altered to express a cytokine stably associated in the cell outer membrane, or the progeny of such a cell, and a pharmaceutical excipient,
formulated for administration to an allogeneic human subject;
which upon administration to a subject is effective in treating a neoplastic disease or eliciting an anti-tumor immunological response in the subject.

32. The composition of claim 31, wherein the cytokine is selected from the group consisting of IL-4, GM-CSF, IL-2, TNF-α, and M-CSF.

33. The composition of claim 31, wherein the cell is a cancer cell.

34. The composition of claim 31, wherein the cell is from a cancer of the same tissue type as a tumor in the subject.

35. The composition of claim 34, wherein the cancer is an ovarian cancer or a brain cancer.

36. The composition of claim 31, wherein the cell is allogeneic to the subject.

~~37. The composition of claim 31, wherein the cell is histocompatibly identical to the subject.~~

38. The composition of claim 31, further comprising a tumor-associated antigen, wherein the combination of the cytokine and the tumor-associated antigen in the composition is effective in treating a neoplastic disease or eliciting an anti-tumor immunological response in the subject.

39. The composition of claim 38, wherein the tumor-associated antigen is obtained from a cell autologous to the subject.

40. The composition of claim 38, wherein the tumor-associated antigen is expressed by the same cells expressing the membrane-associated cytokine.

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41. The composition of claim 38, comprising a combination of:
a) the cell expressing the membrane-associated cytokine; and
b) a tumor cell autologous to the subject;
wherein the combination is effective in treating a neoplastic disease or eliciting an anti-tumor immunological response in the subject.

42. The composition of claim 41, wherein the tumor cell is a primary tumor cell dispersed from a solid tumor obtained from the subject.

43. The composition of claim 41, wherein the tumor cell is a glioma, a glioblastoma, a gliosarcoma, an astrocytoma, or an ovarian cancer cell.

44. The composition of claim 41, wherein the tumor cell is inactivated.

45. The composition of claim 31, wherein the cell expressing the membrane-associated cytokine is inactivated.

46. The composition of claim 31, wherein the cell produces a secreted cytokine in addition to the cytokine stably associated in the outer membrane.

47. The composition of claim 31, wherein a majority of the cytokine produced by the cell is present on the outer membrane of the cell.

48. The composition of claim 38, wherein the cytokine is selected from the group consisting of IL-4, GM-CSF, IL-2, TNF-α, and M-CSF.

49. A composition comprising a tumor associated antigen and a population of cells expressing a transmembrane cytokine at a level sufficient to stimulate an immune response to the tumor associated antigen.

50. A unit dose of the composition according to claim 31, wherein the number of cells is at least about 5×10^6 but not more than about 2×10^8.

51. The composition of claim 31, wherein the cell is a human cell.

52. The composition of claim 31, wherein the cytokine naturally occurs as a membrane 5cytokine.

53. The composition of claim 31, wherein the cytokine is a fusion protein comprising a heterologous transmembrane region.

54. The composition of claim 31, wherein the cell has been transduced with a retroviral expression vector, or is the progeny of such a cell.

55. A method for producing the composition of claim 31, comprising transducing the cell with an expression vector encoding the membrane-associated cytokine.

56. The method of claim 55, wherein the expression vector is a retroviral vector.

57. The method of claim 55, wherein the cytokine is selected from the group consisting of IL-4, GM-CSF, IL-2, TNF-α, and M-CSF.

58. The method of claim 55, wherein the cytokine is expressed under control of a cytomegalovirus (CMV) promoter.

59. The method of claim 55, wherein the cell is from a cancer of the same tissue type as a tumor in the subject.

60. The method of claim 55, wherein the cell is allogeneic to the subject.

61. The method of claim 55, wherein the cell is histocompatibly identical to the subject.

62. A method for producing the composition of claim 38, comprising transducing a cell with an expression vector encoding the membrane-associated cytokine, and providing the transduced cell in combination with the tumor-associated antigen.

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